

Emergence of Complex Dynamics in a Simple Model of Signaling Networks

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ABSTRACT

A variety of physical, social and biological systems generate complex fluctuations with correlations across multiple time scales. In physiologic systems, these long-range correlations are altered with disease and aging. Such correlated fluctuations in living systems have been attributed to the interaction of multiple control systems; however, the mechanisms underlying this behavior remain unknown. Here, we show that a number of distinct classes of dynamical behaviors, including correlated fluctuations characterized by $1/f$ -scaling of their power spectra, can emerge in networks of simple signaling units. We find that under general conditions, complex dynamics can be generated by systems fulfilling two requirements: i) a “small-world” topology and ii) the presence of noise. Our findings support two notable conclusions: first, complex physiologic-like signals can be modeled with a minimal set of components; and second, systems fulfilling conditions (i) and (ii) are robust to some degree of degradation, i.e., they will still be able to generate $1/f$ -dynamics.

Complex systems are typically comprised of a number of interacting units that communicate information and are able to process and withstand a broad range of stresses [1, 2, 3, 4]. In physiology, free-running healthy systems typically generate complex output signals that have long-range correlations—i.e., a $1/f$ -decay of the power spectra for low frequencies¹ [5, 6, 7]. Deviations from the $1/f$ pattern have been associated with disease or aging on a number of contexts [3, 8].

In spite of its practical and fundamental interest [9], the origin of such correlated dynamics remains an unsolved problem [4]. Until recently, attention has focused primarily on the complexity of the specific physiologic sub-systems or on the nature of the nonlinear interactions between them [10, 11, 12]. In particular, Boolean variables, which can take one of two values, 0 or 1, and Boolean functions have been extensively used to model the state and dynamics of complex systems—see [12] for an introduction. The reason such a “simplistic” description may be appropriate arises from the fact that Boolean variables provide good approximations to the nonlinear functions encountered in many control systems [10, 13, 14, 15]. Random Boolean networks (RBNs) were proposed by Kauffman [10] as models of genetic regulatory networks, and have also been studied in a number of other contexts [13, 14]. Wolfram [15], in contrast, proposed that cellular automata (CA) models—a class of ordered Boolean networks with *identical* units—may explain the real-world’s complexity. Neither of these two classes of models has been shown to generate the complex dynamics with $1/f$ -fluctuations observed in healthy physiologic systems.

We propose here a new modeling approach (Fig. 1a) that departs from traditional approaches in that we pay special attention to the *topology* of the network of interactions [4], *and* the role of *noise* [16]. Our model is rooted in two considerations frequently observed in real-world systems: (i) the units in the system are connected mostly locally but also with some long-range connections, giving rise to so-called *small-world* topology [17, 18], and (ii) the interaction between the units is affected by *noisy* communication and/or by noisy stimuli [19, 20, 21, 22, 23]. We demonstrate that simple rules, such as the majority rule, are able to generate signal with complex fluctuations under simple but physiologically-relevant conditions.

Methods

¹ A power law decaying power spectrum $S(f) \propto f^{-\beta}$ is the signature of a signal with power-law decaying correlations. The case $\beta = 2$ corresponds to a Brownian, while $\beta = 0$ corresponds to a completely uncorrelated “white” noise. The intermediate case, $S(f) \propto 1/f$, is a “compromise” between the small time-scale roughness but large time-scale smoothness of white noise and the small time-scale smoothness but large time-scale roughness of Brownian noise.

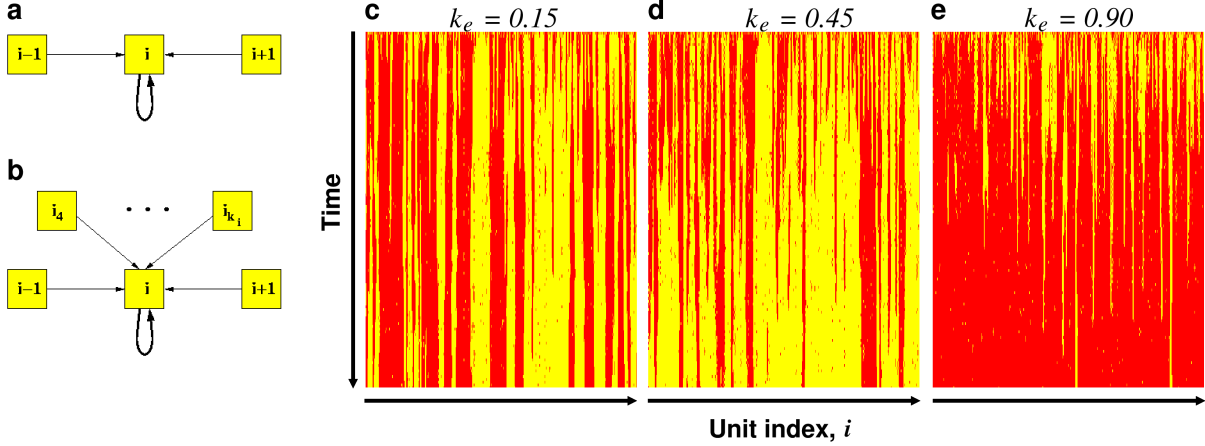


FIG. 1: Emergence of complex dynamics in simple signaling networks. Our model for signaling networks is defined as follows. **a**, The units comprising the network, which are located on the nodes of a one-dimensional lattice, have bi-directional nearest-neighbour connections. **b**, A number $k_e N$ of additional unidirectional links is established between pairs of randomly selected units, where k_e is the mean excess connectivity and N is the number of units in the system. At time $t = 0$, we assign to each unit $i = 1, \dots, N$ a state $\sigma_i(0)$ randomly chosen from the set $\{0, 1\}$ and a Boolean function \mathcal{F}_i ; cf. Eq. (1). This Boolean function (or rule) determines the way the inputs are processed. Each unit effectively processes two inputs, one corresponding to the average state of its neighbours and its own state. With probability η , a unit “reads” a random Boolean variable instead of the state of a neighbour, where the parameter η quantifies the intensity of the noise. Note that the noise does not alter the state of the units, just the value read by its neighbour. At each subsequent time step, each unit updates its state synchronously according to its Boolean function. Time evolution of systems comprising 512 units with $\mathcal{F}_i = 232$ for all units and $\eta = 0.1$, and **c** $k_e = 0.15$, **d** $k_e = 0.45$, **e** $k_e = 0.90$. A red dot indicates $\sigma_i(t) = 1$ while a yellow dot indicates $\sigma_i(t) = 0$. The three panels display the time evolution for systems starting from the same initial configuration and using the same sequence of random numbers. Thus, the difference in the dynamics is due uniquely to the different number of long distance links. For $k_e = 0.15$ the system quickly evolves toward a configuration with several clusters in which all the units are in the same state. The boundaries of these clusters drift due to the noise but the state of the system $S(t)$ is quite stable and the dynamics are close to Brownian noise. In contrast, for $k_e = 0.90$ a large stable cluster develops and the state of the system changes only when some units change state due to the effect of the noise. This process yields white-noise dynamics. For $k_e = 0.45$ clusters are formed but they are no longer stable—unlike what happens for small k_e . In this case, information propagates through the random links which can lead to a change in the state of one or more units inside a cluster. Our results suggest that because these long-range connections exist on all length scales, they lead to long-range correlations in the dynamics and the observed $1/f$ -behavior (Fig. 3b).

The model—We place the Boolean units comprising the network on the nodes of a one-dimensional ring and establish bi-directional nearest-neighbor connections (Fig. 1). Then, we add $k_e N$ additional unidirectional links—where k_e is the mean excess connectivity and N is the number of units in the system—between pairs of randomly selected units. Hence, each unit has a set of links through which incoming signals arrive and that the unit then processes. The state

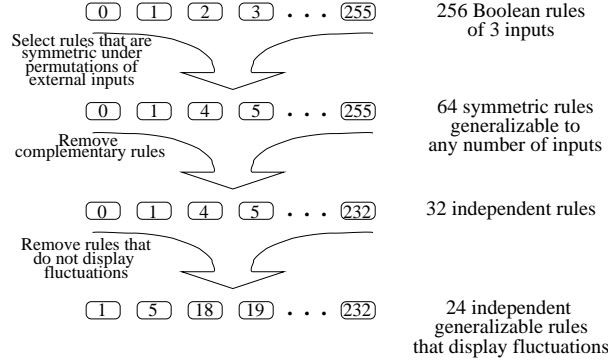


FIG. 2: Selection of Boolean rules for investigation. Our goal is to investigate Boolean functions that display non-trivial dynamics and can be generalized to any number of inputs. To this end, we start from 256 rules of 3 inputs but then restrict our attention to the ones that are symmetric under permutations of the external inputs. This selection results in 64 Boolean rules. However, each rule has another that is its complementary—i.e., display the same dynamics when switching zeros and ones—or inverse—i.e., display the same dynamics when taken every other step. Since these pairs of rules have equivalent dynamics, we need to investigate only 32 independent rules. Of these, eight do not display fluctuations, even in the presence of noise, resulting in 24 independent rules that could present complex fluctuations. The phase-spaces of each of these 24 rules are shown in the Supplementary Material.

of each neighbour is replaced by a random value with probability η —which parameterizes the intensity of the noise.

We assign to each unit $i = 1, \dots, N$ a Boolean function \mathcal{F}_i , which determines the way the states of the neighbors and its own state are processed. We restrict our study to Boolean functions that have only two “effective” inputs: the state of the unit and the average state of all other neighbours. This restriction yields 64 unique symmetric Boolean functions (see Fig. 2 and the Supplementary Material) and it has the advantage that it permits a topology-independent implementation of the Boolean functions, thus enabling a systematic study of the effect of different rules on the dynamics of the system.

Quantification of the dynamical behavior of the system—We start all of our numerical simulations with a random initial configuration and let the system evolve synchronously according to the rules of the model. We define the state $S(t)$ of the system as the sum of the states σ_i of all the Boolean units

$$S(t) = \sum_i \sigma_i(t). \quad (1)$$

We record $S(t)$ during the course of the simulation (see Figs. 3a-c) and quantify the complexity of the time series generated in terms of its auto-correlation function [3]. We apply the detrended

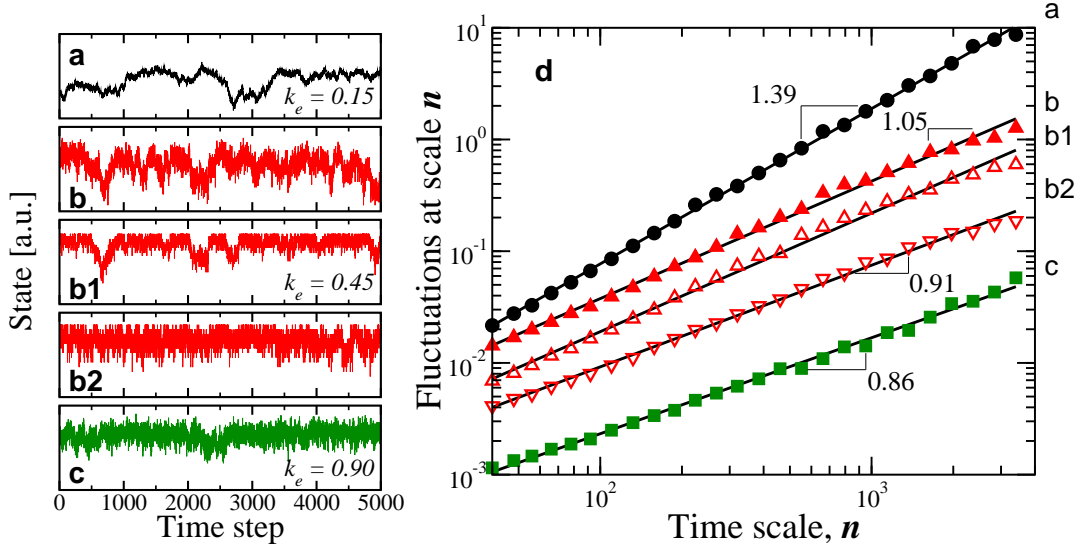


FIG. 3: Quantification of the correlations in the state of Boolean signaling networks. As discussed in the text, we define the state of the system as $S(t) = \sum \sigma_i(t)$. We show $S(t)$ for a system with $N = 4096$ units, $\eta = 0.1$, $\mathcal{F}_i = 232$, and $k_e = 0.90$, $k_e = 0.45$, $k_e = 0.15$. The three values of k_e lead to quite different dynamics of the system. **a**, For a small number of random links, the time correlations display trivial long-range correlations such as found for Brownian noise. **b**, For an intermediate value of k_e , long-range correlations emerge and the power spectrum displays a power-law behavior, $\mathcal{S}(f) \propto 1/f^\beta$, with $\beta \approx 1$. Panels **b1-b2** display the state of the system according to different definitions: In **b1** the state of the system is defined as the sum of the states of a random sample comprising 1/8th of all units, whereas in **b2** the state of the system is defined as the sum of the states of a block of contiguous units comprising 1/8th of the systems. Our results indicate that the evolution of a subset of the population is similar to the dynamics of the whole system. **c**, For a large number of random links, $k_e = 0.90$, the dynamics are less correlated. **d**, Estimation of temporal auto-correlations of the state of the system by the detrended fluctuation analysis (DFA) method [5]. We show the log-log plot of the fluctuations $F(n)$ in the state of the system, versus time scale n for the time series shown in Figs. 3a-c. In such a plot a straight line indicates a power-law dependence $F(n) \propto n^\alpha$. The slope of the lines yields the scaling exponent α , which for a number of physiologic signals from free-running healthy mature systems take values close to one [3]. The exponent α is related to the exponent β of the power spectrum of the fluctuations, $\mathcal{S}(f) \propto 1/f^\beta$, through the relation $\beta = 2\alpha - 1$. The data sets have been shifted upward and the different sets correspond, from top to bottom, to the time series shown in Panels 2a-c.

fluctuation analysis (DFA) method [5] which quantifies long-range time-correlations in the dynamical output of a system by means of a single scaling exponent α (Fig. 3d): Brownian noise yields $\alpha = 1.5$, while uncorrelated white-noise yields $\alpha = 0.5$. For many physiologic signals, one observes $\alpha \approx 1$, corresponding to $1/f$ -behavior, which can be seen as a “trade-off” between the two previous cases [3].

Results

Random Boolean networks—The RBN model corresponds to a completely random network with

randomly selected Boolean rules for the units. As shown in Fig. 4a, we find white-noise dynamics for essentially any pair of values of k_e and η within the ranges considered, suggesting that *even in the presence of noise* a system of random Boolean functions *cannot* generate $1/f$ -dynamics. This result is not unexpected, since the random collection of Boolean functions comprising the system prevents the development of any order or predictability in the dynamics.

CA models with small-world topology and noise—We systematically study the 64 symmetric rules (see Supplementary Material and Fig. 2) for different pairs of values of k_e and η . Some of the rules have parallels to physiologically meaningful dynamics. Rule 232 is a majority rule, that is, each unit will be active next time-step only if the majority of its neighbors is active now. Rule 50 is a threshold rule with refractory time period, that is, whenever the inputs of the neighbors surpass a certain value a unit becomes active in the next time-step and then will be inactive for at least one time-step. The 64 symmetric rules lead to three *qualitatively* distinct phase-spaces (Figs. 4b–d). Rule 232, the majority rule—which is representative of the first type of phase-space—displays three distinct types of dynamical behavior (Fig. 4b): For small k_e , we find mostly Brownian-like scaling. For large k_e , we find mostly white-noise dynamics. Of greatest interest, for intermediate values of k_e and for a broad range of values of the intensity of the noise η , we find $1/f$ -fluctuations.

Rule 50—which is representative of a second type of phase-space—displays fewer types of dynamical behavior. In particular, we find only a narrow range of noise intensities (with a weak dependence on k_e) for which the dynamics display $1/f$ -correlations. For $\eta \gtrsim 0.1$, the dynamics become uncorrelated (Fig. 4c). Rule 160—which is representative the third type of phase-space—displays white-noise dynamics for all values of k_e and η (Fig 4d).

Note that for $k_e = 0$ —i.e., when the network is a one-dimensional lattice—the model is not able to generate $1/f$ -dynamics. This implies that in the context of the model, the existence of long-range connections—i.e., the small-world topology achieved by making $k_e \neq 0$ —is an essential ingredient for the emergence of $1/f$ -dynamics.

Robustness of the findings

In order to determine the generality of the results presented above, one needs to address the questions of how these findings are affected by (i) changes in the topology of the network or (ii) “errors” in the units’ implementation of the rules.

Concerning (i), we note that the network topologies considered so far span the cases of ordered one-dimensional lattices, small-world networks, and random graphs [24]. However, all networks

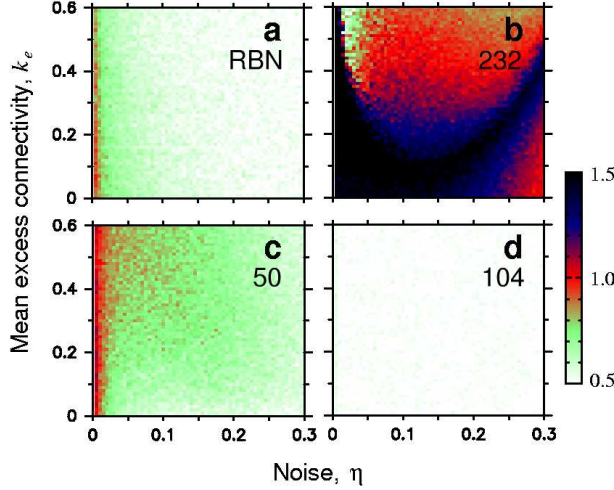


FIG. 4: Systematic evaluation of the correlations in the dynamics generated by different rules. We quantify the long-range correlations in the dynamics by means of the DFA exponent α [5] systematically estimated for time-scales $40 < n < 4000$. We show α for 3,721 pairs of values of k_e and the noise η in the communication between the units comprising the network. For all simulations, we follow the time evolution of systems comprising 4,096 units for a transient period lasting 8,192 time steps, and then record the time evolution of the system for an additional 10,000 time steps. In order to avoid artifacts due to the fact that for some of the rules the units switch states with period 2, we consider in our analysis the state of the systems at every other time step. **a**, Random Boolean network (RBN) as defined by Kauffman [10]. Our results show that the dynamics generated by these systems are generally of the white-noise type with a weak dependence on the noise intensity and no dependence on the number of long-distance links. **b**, Rule 232, a.k.a. the majority rule. This rule is representative of two other rules, numbers 19 and 1. Rule 232 displays a very rich phase-space with a variety of dynamical behaviors, all the way from white noise (represented in white and green) to Brownian noise (represented in black). **c**, Rule 50, a threshold rule with refractory period. This rule is representative of eight other rules, numbers 5, 36, 37, 73, 77, 94, 108, 164. These rules display a relatively simple phase-space with behaviors extending from white noise to $1/f$ -noise. The $1/f$ -behavior is restricted to very small noise intensities and there is a very weak dependence on k_e . **d**, Rule 104. This rule is representative of twelve other rules (see the Supplementary Material). Their phase space is extremely simple, displaying only white noise behavior.

considered are comprised of units with approximately the same degree, i.e., the same number of connections. To investigate the role of the distribution of number of connections, we also study networks which span the range of empirically observed degree distribution: a delta-distribution, an exponential distribution, and a power law distribution. The latter case corresponds to the so-called scale-free networks [18]. Notably, we find that the picture of the phase-space presented in Fig. 4b does not get altered by these changes in the degree distribution (see the Supplementary Material).

In order to address (ii), we systematically explore the dynamical behaviors in the phase-space defined by (k_e, η) for systems composed of units operating according to either rule 232 or a randomly selected rule. Notably, we find that with as many as 1/4th of all units operating according

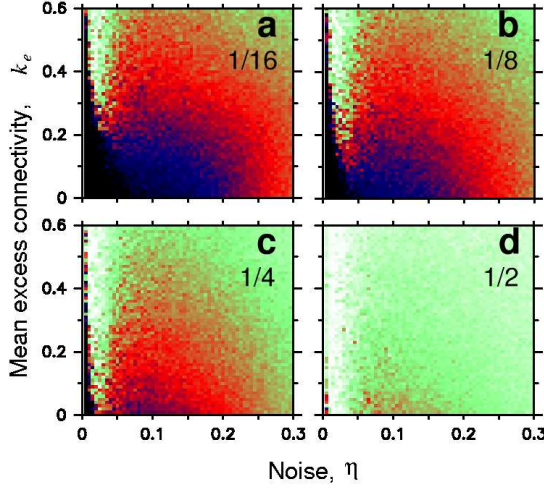


FIG. 5: Phase-space for signaling networks with mixing of Boolean rules. We systematically calculate the exponent α , characterizing the correlations in the dynamics, for systems composed of units operating according to rule 232 but with some fixed fraction of units operating according to a randomly selected symmetric Boolean rule. Each value is an average over 5 independent runs. **a**, 1/16th of the units operating according to a randomly selected rule. **b**, 1/8th of the units operating according to a randomly selected rule. **c**, 1/4th of the units operating according to a randomly selected rule. **d**, 1/2th of the units operating according to a randomly selected rule. These figures suggest that the presence of random Boolean functions leads to a decrease in the richness of the phase space of the systems. Specifically, if more than 1/4th of all the units operate according to randomly selected Boolean functions, then the phase-space displays mostly white-noise dynamics.

to random Boolean functions the model still displays a rich phase-space including white, $1/f$ and Brownian noise (Fig. 5). This finding holds even if instead of using random Boolean functions we consider a single Boolean function (Fig. 6).

Discussion

Our results are notable for a number of reasons. First, they demonstrate that a new model of signaling networks is able to generate a broad range of behaviors reminiscent of those observed in physiologic systems. Second, we show for a rather general class of models that a variety of dynamical behaviors can only emerge under restrictive, but physiologically-relevant assumptions; namely, the system must have a small-world topology, and noise must be present.

An interesting aspect of our results is that some of the rules we consider have plausible physiologic interpretation. For instance, rule 232 is a rule in which a unit changes its state to that of the majority of the incoming inputs. A majority rule appears to be operative in the central nervous system where multiple fibres (excitatory or inhibitory) converge onto a single neuron. Action potentials converging in a neuron summate to bring the neuron to the threshold for firing [25]. A

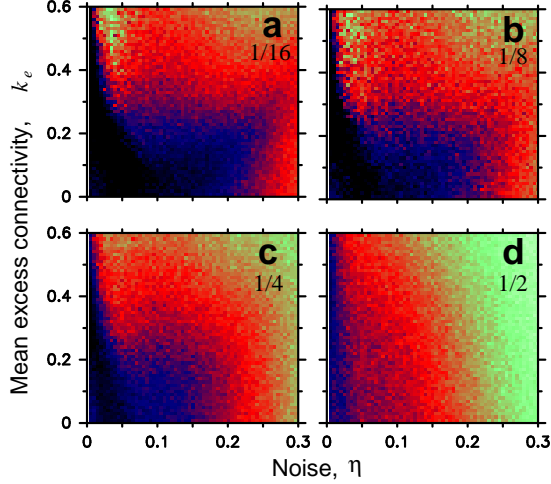


FIG. 6: Phase-space for signalling networks with mixing of two Boolean rules. We systematically calculate the exponent α , characterizing the correlations in the dynamics, for systems composed of units operating according to either rule 232 or rule 50. Each value is an average over 5 independent runs. **a**, 1/16th of the units operating according to rule 50 and 15/16th operating according to rule 232. **c**, 1/8th of the units operating according to rule 50 and 7/8th operating according to rule 232. **d**, 1/4th of the units operating according to rule 50 and 3/4th operating according to rule 232. **e**, 1/2 of the units operating according to rule 50 and 1/2 operating according to rule 232. When both rules are present in the system—and at least 50% of the units operate according to rule 232—we still find several distinct classes of dynamical behaviours, including a wide range of parameter values that generate $1/f$ -noise.

majority rule also appears to be operative in the baroreflex control of the cardiovascular system. The baroreflex is a feedback loop that continuously controls heart rate by modulating the degree of sympathetic and parasympathetic nervous system input to the sinus node of the heart. Changes in heart rate values are determined by whichever input is dominant at the moment [25].

Our results demonstrates that complex fluctuations are present even when a fraction of the units obeys randomly chosen Boolean functions. This suggest that systems comprised of units operating according to the majority will be robust to the removal or failure of units. Additionally, since this complex dynamics does not depend on a scale-free topology, this system do not necessarily displays the vulnerability to targeted attack observed in scale-free networks [26]. In biological systems this robustness could support the “physiologic reserve” enabling an organism to overcome age- or disease-related loss of system components.

Additionally, our findings raise the intriguing possibility that the interactions within physiologic systems and their degradation with aging and pathology may be symbolically mapped as a “walk” on the phase space (k_e, η) . According to this model, $1/f$ -dynamics similar to that found for healthy physiology are generated when noise intensity and connectivity reside in a well-defined range [27].

A loss of complexity with a breakdown of long-range correlations would be anticipated when these parameters assume values outside this range (Fig. 4). Support for this formulation comes from analysis of heart rate dynamics with aging and disease, where connectivity or coupling among system components is likely to be degraded [3, 4, 8]. Similarly, evidence suggests that decreased social connectedness, and the corresponding decrease in “noisy” stimulation, may be associated with increased cardiac mortality and decreased functional recovery from stroke or dementia [28, 29].

In a related way, the development of complex, adaptive dynamics during the maturation of the organism may be accounted for, at least in part, by the evolution of appropriate connections (see [30, 31] for empirical evidence). Our model predicts that the fraction of non-local connections has an optimal range of values; hence, an excessive number of certain types of inputs may also degrade functionality. Our results are thus consistent with empirical evidence suggesting that development and maintenance of healthy function may require adjusting the number of connections. Finally, the model may also provide a robust way to generate fluctuations that closely resemble physiologic signals, which could be implemented in medical devices such as mechanical ventilators [32, 33] and hormone infusion pumps [34].

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